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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,905	07/15/2003	Karim Boumediene	065691-0327	7317

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EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,905	BOUMEDIENE ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-68* is/are rejected.

7)☒ Claim(s) *57-68* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's request for reconsideration of the rejection under 35 USC 102, during the interview of 7/17/2008, is persuasive and, therefore, the finality of the Office Action of 12/7/2007 is withdrawn.

The request is based on the argument that inherency may not be established by probabilities or possibilities, as outlined in MPEP 2112, section IV, (see arguments on p. 6, last paragraph - p. 7, 2nd paragraph of the 4/7/2008 reply). Since this argument is persuasive, the finality of the prior Office Action has been withdrawn.

2. Applicant's arguments, see pp. 6-7, filed 4/7/2008, with respect to rejection under 35 USC 102 as anticipated by Maheu et al. have been fully considered and are persuasive. The rejection of claims 57-63, 66 and 68 has been withdrawn.

The rejection has been withdrawn because applicant's arguments that inherency may not be established by probabilities or possibilities are persuasive.

3. As pointed out in the Advisory Action of 4/7/2008, applicant's arguments, see p. 12, filed 4/7/2008, with respect to the rejection under 35 USC 112, 1st paragraph have been fully considered and are persuasive. The rejection of claims 60-61 has been withdrawn.

4. Applicant's arguments with respect to the rejection of claims 57, 64-65 and 67 under 35 USC 103 have been considered but are moot in view of the new ground(s) of rejection.

In view of the withdrawal of the rejection under 35 USC 102, on which the rejection of claim 57 under 35 USC 103 in the 12/7/2008 Office Action was based, the prior rejection is now considered insufficient and is therefore withdrawn. The prior rejections are replaced by the following objections and rejections.

Claim Objections

5. Claims 57-68 are objected to because of the following informalities: the phrase "to person" in line 3 of claim 57 is grammatically incorrect. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 57-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rancurel (US 5,498411; cited in a prior Office Action); Maheu, et al. ("Symptomatic Efficacy of Avocado/Soybean Unsaponifiables in the Treatment of Osteoarthritis of the Knee and Hip"; 1998 Jan; Arthritis & Rheumatism; 41(1); 81-91; cited in a prior Office Action); Woolf, et al. ("Burden of major musculoskeletal conditions: 2003; Bulletin of the World Health Organization 81:646-656; cited in a prior Office Action); and.

Rancurel teaches a method of preparing nonsaponifiable matter of avocado oil (title; abstract) and similar extracts of soya bean oil is compared (col. 1, lines 45-52); the nonsaponifiable matter may be used as an active ingredient in pharmaceutical or food industries and provides comfort in the elderly in particular (col. 1, lines 33-38). Rancurel does not teach the combination of an unsaponifiable component of avocado oil together with an unsaponifiable component of soya bean oil, nor either component administered in the treatment of osteoporosis. Maheu teaches a clinical trial of avocado/soybean unsaponifiables (ASU) in the treatment of patients with symptomatic osteoarthritis of the knee or hip (title; Objective); ASU are made of unsaponifiable fractions of 1/3 avocado oil and 2/3 soybean oil (weight ratio avocado/soy is 0.5; p. 82, 2nd paragraph); 63 women with a mean age of 63.3 received ASU treatment (Table 1, p. 85); 300 mg

capsules of ASU were administered orally (p. 83, 1st paragraph); safety was determined to be good with no severe side effect and no difference between ASU and placebo were noted (p. 90, 3rd paragraph). Woolf teaches osteoarthritis affects 18% of women age >60 years (abstract) and 30% of postmenopausal white women in the USA are estimated to have osteroporosis in at least one skeletal site (p. 651, 1st paragraph); in the United Kingdom the estimate is that around 23% of women aged 50 years or greater have osteoporosis (p. 651, 1st paragraph); percentages increase with age, up to 50% of women at 85 years of age that have osteoporosis (Figure 3; Table 3; p. 651, 1st paragraph). The number of women with both conditions in the Maheu trial may be calculated as (0.18 x 0.30 x 63 = 3.4) or (0.18 x 0.23 x 63 = 2.6); the average of these two calculations, taken as the minimum estimated number of women in the Maheu clinical trial with osteoporosis, is 3. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the combination of ASU in the form of a capsule, as taught in the Maheu trial (a drug form), or in the form of a food additive to women with osteoporosis, especially to the older women, about 1/2 of which have osteoporosis at age 85. The motivation to administer to the specific subpopulation of older women with osteoporosis would have been application of the teaching of Rancurel, that nonsaponifiable matter of avocado and soya bean oils provide comfort to the elderly in particular, to elderly women with osteoporosis. Providing the ASU in the form of a food additive in the proportions taught in claim 65 would also have been obvious to one of ordinary skill in the art at the time of the invention; administration of the 300 mg dose taught by Maheu in 1.5-300 g food corresponds to the percentages of

instant claim 65. A single serving of food or a drink of juice would fall within the proportion range of the claim and deliver the doses taught by Maheu. The motivation would have been the convenient delivery of the proper amount of the ASU in food as a carrier to elderly individuals that find it difficult to take pills.

Absent evidence to the contrary, the ASU taught by Maheu would contain at least one unsaponifiable component from "dry" avocado oil, and the components recited in claims 60-63 would also be present. As previously pointed out, a fraction enriched with the furan compounds taught by Farines, et al. (JAOCS; 1995; 72(4): 473-476; IDS 9/6/2007 reference B2) would be contained in the avocado unsaponifiable component.

9. Claims 57-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bourmediene et al. ("Avocado/Soya Unsaponifiables Enhance the Expression of Transforming Growth Factor β1 and β2 in Cultured Articular Chondrocytes; 1999 Jan; Arthritis & Rheumatism; 42(1): 148-156); Maheu, et al. ("Symptomatic Efficacy of Avocado/Soybean Unsaponifiables in the Treatment of Osteoarthritis of the Knee and Hip"; 1998 Jan; Arthritis & Rheumatism; 41(1); 81-91; cited in a prior Office Action); and either one of the following: Kim et al. ("Mechanisms of action of the soy isoflavone genistein: emerging role for its effects via transforming growth factor-β signaling pathways"; 1998 Dec; Am. J. Clin, Nutr.; 68(suppl): 14185-255; IDS 10/21/2003 reference A13) or Marie ("Growth factors and bone formation in osteoporosis: roles for IGF-I and TGF-β"; 1997 Jan.; Rev. Rhum. Engl. Ed.; 64(1): 44-53; abstract; PMID: 9051859).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

It is noted that the Bourmediene article was published after the foreign priority date (the Kim article was published the same month as the foreign application); no translation has been provided to overcome these intervening references. However, the Bourmediene article acknowledges that the research was presented in part at the 60th Annual Scientific Meeting of the American College of Rheumatology, in October 1996, more than one year prior to the application and priority dates (see 1st footnote on the bottom left column of p. 148). This indicates the teaching was known by others before the invention (i.e., more than one author is different from the instant application indicating the reference is "by others"); and the teaching was in public use at least one year before the date of application.

Boumediene teaches that avocado and soya unsaponifiables (ASU) have been reported to exert beneficial effects in the treatment of periodontal and osteoarticular diseases, and stimulate deposition and repair of extracellular matrix components (abstract); ASU are composed of unsaponifiable fractions of avocado and soybean oils at a ratio of 1:2/3, respectively (p. 149, 3rd paragraph); the ASU-induced stimulation of matrix synthesis previously reported in cultured chondrocytes could be explained by the ability to enhance TGFβ expression in these cells; stimulation of the expression of TGFβ1, TGFβ2 and PAI-1 is taught (abstract). Bourmediene does not teach administration of ASU for treating osteoporosis, oral composition, use as a food

additive, or composition forms. Kim teaches the soy isoflavone genistein is a large component of soybeans and most soy products (p. 1418S, last paragraph); genistein acts as an enhancer of TGFβ (abstract; p. 1419S, 2nd paragraph); there is a direct link between genistein and TGFβ1activity (p. 1420S, 2nd-5th paragraphs); administration is taught as a soy based beverage (p. 1420S, right, 2nd paragraph); a genistein-containing, soy-based diet ameliorated the loss of bone density in ovariectomized rats and pure genistein inhibits osteoclast function, attenuation of bone loss by soy or genistein may be due to enhancement of TGFβ1 (p. 1421S, 3rd - 4th paragraphs). Marie teaches the cellular mechanisms involved in osteoblast function and bone formation alterations have been partially elucidated; bone loss related to aging or unloading is characterized by diminished osteoblast proliferation and reduced local concentrations of IGFs and TGF-beta, which modulate the proliferation and activity of bone-forming cells; preventative or curative treatment with growth factors may be beneficial in osteopenia due predominantly to decreased bone formation, low doses of TGF-beta have been reported to increase osteoblast recruitment and differentiation, leading to enhanced trabecular bone formation and decreased bone loss in models of osteopenia induced by aging, estrogen deficiency and unloading, clinical trials also suggest that low doses of growth factors may stimulate bone formation, progress awaits factors of analogs that are capable of locally and specifically increasing osteoblast recruitment and differentiation without inducing side-effects (abstract). Maheu teaches a clinical trial of avocado/soybean unsaponifiables (ASU) in the treatment of patients with symptomatic osteoarthritis of the knee or hip (title; Objective); ASU are made of unsaponifiable

fractions of 1/3 avocado oil and 2/3 soybean oil (weight ratio avocado/soy is 0.5; p. 82, 2nd paragraph); ASU stimulates TGFβ1 and plasminogen activator inhibitor 1 (p. 82, 2nd paragraph); 63 women with a mean age of 63.3 received ASU treatment (Table 1, p. 85); 300 mg capsules of ASU were administered orally (p. 83, 1st paragraph); safety was determined to be good with no severe side effect and no difference between ASU and placebo were noted (p. 90, 3rd paragraph). It would have been obvious to one of ordinary skill in the art to administer ASU, either in the form of a food additive or in the form of a capsule (drug form) to a person for the treatment of osteoporosis. The motivation would have been the activity of enhancing TGFβ expression by ASU applied to osteoporosis, since both Kim and Marie indicate that higher TGFβ levels have beneficial effects in limiting bone loss and increasing bone formation in osteoporosis. The proportions taught in claim 65 would also have been obvious to one of ordinary skill in the art at the time of the invention; administration of the 300 mg dose taught by Maheu in 1.5-300 g food corresponds to the percentages of instant claim 65. A single serving of food or a drink of juice would fall within the proportion range of the claim and deliver the doses taught by Maheu. The motivation would have been the convenient delivery of the proper amount of the ASU in food as a carrier, especially for administration to elderly individuals that may find taking capsules difficult.

Absent evidence to the contrary, the ASU taught by Boumediene and/or Maheu would contain at least one unsaponifiable component from "dry" avocado oil, and the components recited in claims 60-63 would also be present.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614